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<p>(54) Title: ANGIOSTATIC COMPOUNDS</p> <p>(57) Abstract</p> <p>The present invention is directed to compositions containing chroman-type or benzofuran type compounds and methods for their use in preventing pathological neovascularization.</p>		

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ANGIOSTATIC COMPOUNDS

Background of the invention

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The present invention relates to certain compounds useful in preventing and treating neovascularization. Specifically, the invention is directed to compositions containing chroman-type compounds and methods to treat neovascularization.

Angiogenesis is a term used to describe the development of new blood vessels or
15 neovascularization (L. Diaz-Flores et al., *Angiogenesis: an Update, Histology and Histopathology*, volume 9, pages 807-843 (1994)). Though angiogenesis is a normal process for the development or maintenance of the vasculature, pathological conditions (i.e., angiogenesis dependent diseases) arise where blood vessel growth is actually harmful. Such pathologies include diabetic retinopathies, proliferative vitreoretinopathies, psoriasis,
20 arthritis and tumor development. The progression of angiogenesis occurs in several phases which include: elaboration of the angiogenic signal; dissolution of the blood vessel basement membrane; endothelial cell proliferation; endothelial cell migration; and formation and differentiation of capillary tubules and loops. Each of these phases is a potential target for pharmacological intervention.

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Tumor growth is dependent on neovascularization. For solid tumors to grow beyond the size of a pea, they must become vascularized. They do so by secreting their

own angiogenic factor(s) which recruit new blood vessels to provide essential nutrients and oxygen.

Angiogenesis is also associated with important diseases of ocular tissue especially in older patients and diabetics. Any abnormal growth of blood vessels in the eye can scatter and block the incident light prior to reaching the retina. Neovascularization can occur at almost any site in the eye and significantly alter ocular tissue function. Some of the most threatening ocular neovascular diseases are those which involve the retina. For example, many diabetic patients develop a retinopathy which is characterized by the formation of leaky, new blood vessels on the anterior surface of the retina and in the vitreous causing proliferative vitreoretinopathy. A subset of patients with age related macular degeneration develop subretinal neovascularization which leads to their eventual blindness.

Another area involving neovascularization and unwanted tissue growth involves the technique of glaucoma filtration surgery. With this technique, a small fistula or bleb is surgically formed in the eye to facilitate drainage of aqueous humor, and therefore reduce the intraocular pressure of the eye. This technique can be frustrated, however, by the closure of the bleb. The bleb, which is a tissue wound in the eye, has a tendency to close up due to normal healing processes involving the addition of fibroblasts and/or neovasculature. Therefore, an agent which inhibits bleb vascularization and fibroblast proliferation would be useful in maintaining bleb patency.

Current therapy for the treatment of ocular neovascular disease is not very effective. Retinal neovascularization is often treated with multiple laser burns to the retina to remove the pathological vasculature. Patients with neovascular diseases of the anterior chamber

(e.g. corneal neovascularization, iritis rubeosis) are treated with potent topical ocular glucocorticoids. These therapies are only partially effective and generally only slow neovascularization and the progress of the overall disease. In addition, they can cause severe side effects if used over a relatively long period of time.

5 Other attempts have been made to provide therapies for the prevention or treatment of pathological angiogenesis. For example, angiostatic steroids functioning to inhibit angiogenesis in the presence of heparin or specific heparin fragments are disclosed in Crum, et al., *A New Class of Steroids Inhibits Angiogenesis in the Presence of Heparin or a Heparin Fragment*, Science, volume 230, pages 1375-1378 (1985). Another group of
10 angiostatic steroids useful in inhibiting angiogenesis is disclosed in commonly assigned United States Patent No. 5,371,078 (Clark et al.).

Glucocorticoids, as mentioned above, have also been shown to inhibit angiogenesis. However, the use of glucocorticoid therapy in general is complicated by the inherent problems associated with steroid applications. Such problems include elevated intraocular
15 pressure (Kitazawa, *Increased Intraocular Pressure Induced by Corticosteroids*, American Journal of Ophthalmology, volume 82, pages 492-493 (1976)).

Still other therapies have included: the use of protamine (S. Taylor, *Protamine is an Inhibitor of Angiogenesis*, Nature, volume 297, pages 307-312 (1982)); the use of calcitriol (European Journal of Pharmacology, volume 178, pages 247-250 (1990)); and the use of
20 the antibiotic, fumagillin and its analogs, disclosed in EP 354787. The use of a variety of pharmaceutical proteins has also been proposed for treating angiogenesis. Such therapies have included: monoclonal antibodies directed to fibroblast growth factor, disclosed in WO

9106668; platelet factor 4, disclosed in WO 9302192; and thrombospondin fragments, disclosed in WO 9316716.

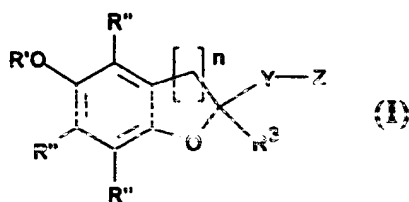
Summary of the Invention

5 This invention is directed to compositions containing angiostatic compounds and methods of using these compositions to prevent and/or treat neovascularization in human patients. In particular, the compositions are useful for controlling ocular neovascularization. Additionally, the compounds are useful in treating glaucoma filtration bleb failure, pterygium, hyperkeratosis, cheloid formation and polyp formation.

10 The compositions of the present invention also have the advantage of providing effective angiostatic therapy which avoids the problems inherent in steroid therapies.

Detailed Description of the Invention

The compositions of the present invention contain compounds which have the
15 general formula (I):



wherein:

n is 1 or 2;

R is H, C₁-C₆ alkyl or C₃-C₆ cycloalkyl;

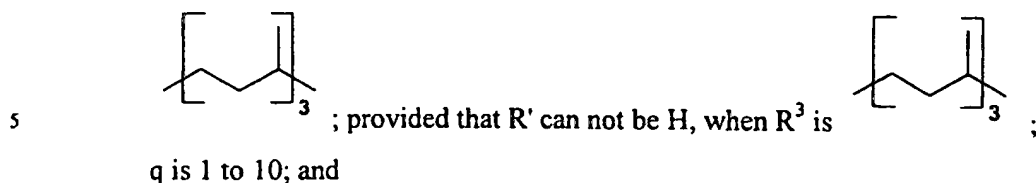
Y is H, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, O, NR, C(R)₂, CH(OH) or S(O)_{n'};

n' is 0 to 2;

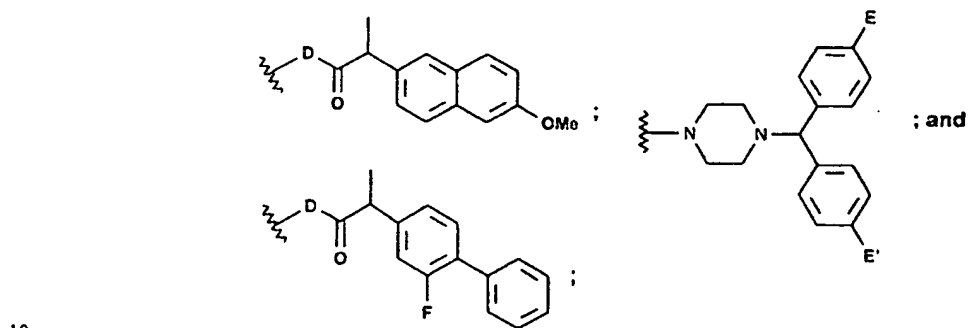
R' is H, C(O)R, C(O)N(R)₂, PO₃⁻, SO₃⁻, or HO₂C(CH₂)₂(C=O)---;

R'' is H or C₁-C₆ alkyl;

R³ is H, C₁-C₆ alkyl, (CH₂)_q(OH), ---(C=O)O(CH₂)_qCH₃ or



Z, if present, is H, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, or selected from the group consisting of:



wherein:

D is O or NR; and

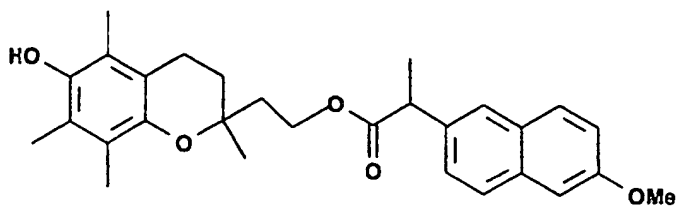
E and E' are independently H, F or Cl.

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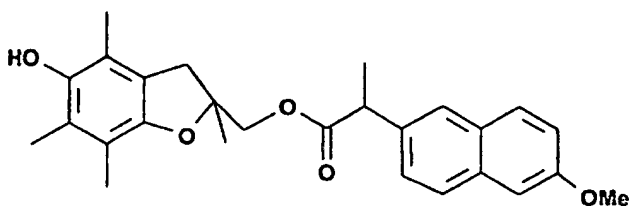
The compounds of the present invention also include pharmaceutically acceptable salts of the compounds of formula (I)

The following compounds are particularly preferred for use in the compositions and methods of the present invention:

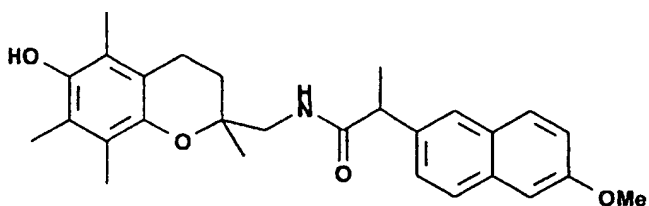
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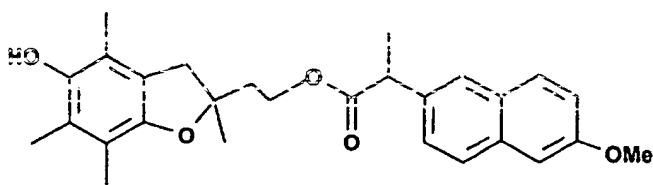
2-(6-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-benzo[1,2-b]pyran-2-yl)ethyl 2-(6-methoxy-2-naphthyl)propionate ("Compound A");



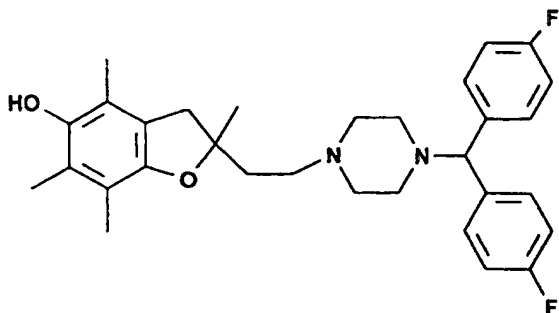
5 2-(5-hydroxy-2,4,6,7-tetramethyl-2,3-dihydro-benzo[1,2-b]furan-2-yl)methyl 2-(6-methoxy-2-naphthyl)propionate ("Compound B");



10 N-(2-(6-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-benzo[1,2-b]pyran-2-yl)methyl) 2-(6-methoxy-2-naphthyl)propionamide ("Compound C");

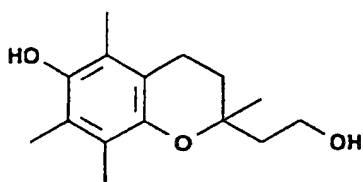


15 2-(5-hydroxy-2,4,6,7-tetramethyl-2,3-dihydro-benzo[1,2-b]furan-2-yl)ethyl 2-(6-methoxy-2-naphthyl)propionate ("Compound D");



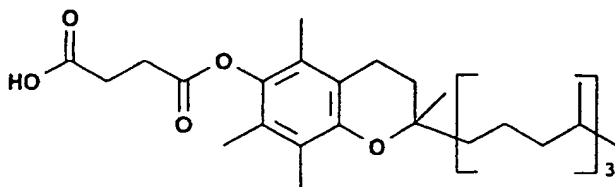
1-[2-(5-hydroxy-2,4,6,7-tetramethyl-2,3-dihydro-benzo[1,2-b]furan-2-yl)2-ethyl]-4-[4,4'-fluorobenzhydryl]piperzine ("Compound E")

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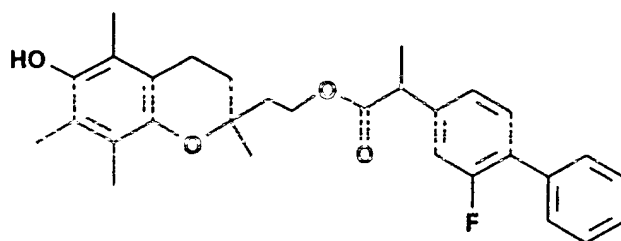


2-(6-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-benzo[1,2-b]pyran-2-yl)ethanol ("Compound F")

10



Vitamin E succinate (VES) ("Compound G")



15 2-(6-hydroxy-2,5,7,8-tetramethyl-2,3-dihydro-2H-benzo[1,2-b]pyran-2-yl)ethyl 2-(3-fluoro-4-phenyl-phenyl)propionate ("Compound H").

The initiation of new blood vessel formation may arise quite differently in various tissues or as a result of different diseases. Many substances have been found to induce neovascularization, see, Folkman, et al., *Angiogenic Factors*, Science, volume 235, pages 442-447 (1987). However, it is believed, that once initiated, the process of
5 neovascularization is similar in all tissues regardless of the associated disease, Furcht, *Critical Factors Controlling Angiogenesis: Cell Products, Cell Matrix, and Growth Factors*, Laboratory Investigation, volume 55, No. 5, pages 505-509 (1986).

There are many theories associated with the cause of neovascularization, and there may be different inducers depending on the disease or surgery involved, BenEzra,
10 *Neovascularogenic Ability of Prostaglandins, Growth Factors, and Synthetic Chemoattractants*, American Journal of Ophthalmology, volume 86, No. 4, pages 455-461, (October, 1978). Regardless of the cause or the associated disease, it is believed that angiostatic agents work by inhibiting one or more steps in the process of neovascularization. Therefore, the angiostatic compounds of this invention are useful in
15 the treatment and prevention of neovascularization associated with a variety of diseases and surgical complications.

The angiostatic compositions of the present invention are useful in inhibiting pathological neovascularization in human patients. As used herein, the term "pathological neovascularization" refers to those conditions where the formation of blood vessels
20 (neovascularization) is harmful to the patient. Examples of pathological neovascularization dependent diseases include: head trauma, spinal trauma, systemic or traumatic shock, stroke, hemorrhagic shock, cancer, arthritis, arteriosclerosis, angiofibroma, arteriovenous malformations, corneal graft neovascularization, delayed wound healing, diabetic

retinopathy, granulations, burns, hemangioma, hemophilic joints, hypertrophic scars, ocular neovascularization, nonunion fractures, Osler-Weber Syndrome, psoriasis, pyogenic granuloma, retrolental fibroplasia, pterigium, scleroderma, trachoma, vascular adhesions, and solid tumor growth.

5 In particular, the compositions are useful in preventing and treating any ocular neovascularization, including, but not limited to: retinal diseases (diabetic retinopathy, chronic glaucoma, retinal detachment, sickle cell retinopathy and subretinal neovascularization due to senile macular degeneration); rubeosis iritis; proliferative vitreo-retinopathy; inflammatory diseases; chronic uveitis; neoplasms (retinoblastoma, 10 pseudoglioma and melanoma); Fuchs' heterochromic iridocyclitis; neovascular glaucoma; corneal neovascularization (inflammatory, transplantation and developmental hypoplasia of the iris); neovascularization following a combined vitrectomy and lensectomy; vascular diseases (retinal ischemia, choroidal vascular insufficiency, choroidal thrombosis and carotid artery ischemia); neovascularization of the optic nerve; and neovascularization due 15 to penetration of the eye or contusive ocular injury.

The use of the compositions of the present invention to ameliorate complications arising from glaucoma filtration surgery is a particularly important aspect of the invention. Glaucoma filtration surgery involves the surgical creation of a fistula with a conjunctival flap which allows the direct drainage of aqueous humor from the anterior chamber into the 20 conjunctival tissue, thereby lowering the elevated intraocular pressure associated with glaucoma. However, in many patients, the filtration "bleb" becomes scarred or healed over so that aqueous drainage can no longer occur. It has been noted that failing filtration blebs may become vascularized prior to failure. This vascularization may feed the fibroblasts

which migrate, proliferate, and block the bleb, or the vascularization itself may also result in physical blockage of the bleb. It is therefore likely that inhibition of filtration bleb neovascularization may inhibit filtration bleb failure.

Additionally the angiostatic agents of the present invention are useful in treating
5 pterygium (primary and recurrent), hyperkeratosis, cheloid formation and polyp formation.

The compounds of formula (I) may be contained in various types of pharmaceutical compositions, in accordance with formulation techniques known to those skilled in the art. For example, the compounds may be included in tablets, capsules, solutions, suspensions and other dosage forms adapted for oral administration; solutions and suspensions adapted
10 for parenteral use; solutions, suspensions and gels adapted for topical ophthalmic use; solutions and suspensions adapted for intra-vitreous or intra-cameral use; and suppositories for rectal use. Solutions, suspensions and other dosage forms adapted for topical application to the involved tissues, such as tissue irrigating solutions, are particularly preferred for treatment of acute conditions associated with surgery or other forms of
15 trauma.

The present invention is particularly directed to the provision of compositions adapted for treatment of ophthalmic tissues. The ophthalmic compositions of the present invention will include one or more compounds of formula (I) and a pharmaceutically acceptable vehicle for said compound(s). Various types of vehicles may be used. The
20 vehicles will generally be aqueous in nature. Aqueous solutions are generally preferred, based on ease of formulation, as well as a patients' ability to easily administer such compositions by means of instilling one to two drops of the solutions in the affected eyes. However, the compounds of formula (I) may also be readily incorporated into other types

of compositions, such as suspensions, viscous or semi-viscous gels or other types of solid or semi-solid compositions. Suspensions may be preferred for compounds of formula (I) which are relatively insoluble in water. The ophthalmic compositions of the present invention may also include various other ingredients, such as buffers, preservatives, co-solvents and viscosity building agents.

An appropriate buffer system (e.g., sodium phosphate, sodium acetate or sodium borate) may be added to prevent pH drift under storage conditions.

Ophthalmic products are typically packaged in multidose form. Preservatives are thus required to prevent microbial contamination during use. Suitable preservatives include: benzalkonium chloride, thimerosal, chlorobutanol, methyl paraben, propyl paraben, phenylethyl alcohol, edetate disodium, sorbic acid, polyquaternium-1, or other agents known to those skilled in the art. Such preservatives are typically employed at a level of from 0.001 to 1.0 percent by weight, based on the total weight of the composition (wt.%).

Some of the compounds of formula (I) may have limited solubility in water and therefore may require a surfactant or other appropriate co-solvent in the composition. Such co-solvents include: polyethoxylated castor oils, Polysorbate 20, 60 and 80; Pluronic® F-68, F-64 and P-103 (BASF Corp., Parsippany NJ, USA); cyclodextrin; or other agents known to those skilled in the art. Such co-solvents are typically employed at a level of from 0.01 to 2 wt.%.

Viscosity greater than that of simple aqueous solutions may be desirable to increase ocular absorption of the active compound, to decrease variability in dispensing the formulations, to decrease physical separation of components of a suspension or emulsion of

formulation and/or otherwise to improve the ophthalmic formulation. Such viscosity building agents include, for example, polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxypropyl cellulose or other agents known to those skilled in the art. Such agents are typically employed at a level of from 0.01 to 2 wt.%. 5

The route of administration (e.g., topical, parenteral or oral) and the dosage regimen will be determined by skilled clinicians, based on factors such as the exact nature of the condition being treated, the severity of the condition, the age and general physical condition of the patient, and so on.

10 As indicated above, use of the compounds of formula (I) to prevent or reduce angiogenesis in ophthalmic tissues is a particularly important aspect of the present invention. The compounds may also be used as an adjunct to ophthalmic surgery, such as by vitreal or subconjunctival injection following ophthalmic surgery. The compounds may be used for acute treatment of temporary conditions, or may be administered chronically, 15 especially in the case of degenerative disease. The compounds may also be used prophylactically, especially prior to ocular surgery or noninvasive ophthalmic procedures, or other types of surgery.

The use of physiologically balanced irrigating solutions as pharmaceutical vehicles for the compounds of formula (I) is preferred when the compositions are administered 20 intraocularly. As used herein, the term "physiologically balanced irrigating solution" means a solution which is adapted to maintain the physical structure and function of tissues during invasive or noninvasive medical procedures. This type of solution will typically contain electrolytes, such as sodium, potassium, calcium, magnesium and/or chloride; an

energy source, such as dextrose; and a buffer to maintain the pH of the solution at or near physiological levels. Various solutions of this type are known (e.g., Lactated Ringers Solution). BSS® Sterile Irrigating Solution and BSS Plus® Sterile Intraocular Irrigating Solution (Alcon Laboratories, Inc., Fort Worth, Texas, USA) are examples of
5 physiologically balanced intraocular irrigating solutions. The latter type of solution is described in United States Patent No. 4,550,022 (Garabedian, et al.), the entire contents of which are hereby incorporated in the present specification by reference.

The specific type of formulation selected will depend on various factors, such as the compound or its salt being used, the dosage frequency, and the disease being treated.
10 Topical aqueous solutions, suspensions, ointments, creams and gels are the preferred dosage forms for the treatment of pterygium, hyperkeratosis, and cheloid and polyp formation. Topical ophthalmic formulations are suitable for preventing glaucoma filtration bleb failure or scar formation associated with ophthalmic surgery.

In general, the doses utilized for the above described purposes will vary, but will be
15 in an effective amount to inhibit or reduce neovascularization. As used herein, the term "pharmaceutically effective amount" to inhibit or reduce neovascularization, is that amount which inhibits formation of new blood vessels or reduces the number of blood vessels which are involved in the pathological condition. The angiostatic compounds will normally be contained in these formulations in an amount from about 0.01 to about 10.0
20 weight/percent. Preferable concentrations range from about 0.1 to about 5.0 weight/percent. Thus, for topical administration, these formulations are delivered to the disease site one to six times a day, depending on the routine discretion of the skilled clinician. Systemic administration, for example, in the form of tablets or suppositories is

useful for the treatment of polyp formation. Tablets containing 10-1000 mg of a compound can be taken 2-3 times per day depending on the discretion of the skilled clinician.

The compositions of the present invention are further illustrated by the following examples.

5

Example 1

Topical compositions useful for controlling ocular neovascularization:

10

Component	wt. %
Angiostatic Compound	0.005-5.0
Tyloxapol	0.01-0.05
HPMC	0.5
Benzalkonium Chloride	0.01
Sodium Chloride	0.8
Edetate Disodium	0.01
NaOH/HCl	q.s. pH 7.4
Purified Water	q.s. 100 mL

Example 2

A preferred topical composition useful for controlling neovascularization:

Component	wt. %
Compound A	1.0
Tyloxapol	0.01-0.05
HPMC	0.5
Benzalkonium Chloride	0.01
Sodium Chloride	0.8
Edetate Disodium	0.01
NaOH/HCl	q.s. pH 7.4
Purified Water	q.s. 100 mL

5

The above formulation is prepared by first placing a portion of the purified water into a beaker and heating to 90°C. The hydroxypropylmethylcellulose (HPMC) is then added to the heated water and mixed by means of vigorous vortex stirring until all of the HPMC is dispersed. The resulting mixture is then allowed to cool while undergoing mixing in order to hydrate the HPMC. The resulting solution is then sterilized by means of autoclaving in a vessel having a liquid inlet and a hydrophobic, sterile air vent filter.

The sodium chloride and the edetate disodium are then added to a second portion of the purified water and dissolved. The benzalkonium chloride is then added to the solution, and the pH of the solution is adjusted to 7.4 with 0.1M NaOH/HCl. The solution is then sterilized by means of filtration.

Compound A is sterilized by either dry heat or ethylene oxide. If ethylene oxide sterilization is selected, aeration for at least 72 hours at 50°C. is necessary. The sterilized angiogenic compound is weighed aseptically and placed into a pressurized ballmill container. The tyloxapol, in sterilized aqueous solution form, is then added to the ballmill container. Sterilized glass balls are then added to the container and the contents of the container are

milled aseptically at 225 rpm for 16 hours, or until all particles are in the range of approximately 5 microns.

Under aseptic conditions, the micronized drug suspension formed by means of the preceding step is then poured into the HPMC solution with mixing. The ballmill container
5 and balls contained therein are then rinsed with a portion of the solution containing the sodium chloride, the edetate disodium and benzalkonium chloride. The rinse is then added aseptically to the HPMC solution. The final volume of the solution is then adjusted with purified water and, if necessary, the pH of the solution is adjusted to pH 7.4 with NaOH/HCl.

10

Example 3

Formulation for oral administration:

15

Tablet:

10-1000 mg of an angiostatic compound with inactive ingredients such as starch, lactose and magnesium stearate can be formulated according to procedures known to those skilled in the art of tablet formulation.

Example 4

Formulation for sterile intraocular injection:

Component	each mL contains:
Angiostatic Compound	10-100 mg
Sodium Chloride	7.14 mg
Potassium Chloride	0.38 mg
Calcium chloride dihydrate	0.154 mg
Magnesium chloride hexahydrate	0.2 mg
Dried sodium phosphate	0.42 mg
Sodium bicarbonate	2.1 mg
Dextrose	0.92 mg
Hydrochloric acid or sodium hydroxide	q.s., pH to approx. 7.2
Water for injection	q.s.

Example 5

Preferred formulation for a topical ocular solution:

Component	wt. %
Compound A	1.0%
Benzalkonium chloride	0.01%
HPMC	0.5%
Sodium chloride	0.8%
Sodium phosphate	0.28%
Edetate disodium	0.01%
NaOH/HCl	q.s. pH 7.2
Purified Water	q.s. 100 mL

5

Example 6

10 A preferred formulation for oral administration:

Tablet:

5-100 mg of Compound A with inactive ingredients such as starch, lactose and magnesium stearate can be formulated according to procedures known to those skilled in the art of tablet formulation.

15

Example 7

Formulations for topical dermatological use:

5 Cream: 1 mg/g of an angiostatic compound in cream base of purified water, emulsifying wax, propylene glycol, stearic acid, isopropyl palmitate, synthetic beeswax, polysorbate 60, potassium sorbate, sorbic acid, propyl gallate, citric acid, and sodium hydroxide.

10 Ointment: 1 mg/g of an angiostatic compound in base of mineral oil and polyethylene.

Example 8

15

Formulation for suppository:

10-500 mg of an angiostatic compound with the following inactive ingredients: glycerin, butylateal hydroxytoluene, butylated hydroxyanisole, edetic acid, polyethylene
20 glycol, and sodium chloride.

The compositions and methods of the present invention are further illustrated by the following in vitro and in vivo biological activity examples of the compounds of formula

(I):

25

Example 9

Representative compounds of the present invention were assayed for their efficacy in inhibiting endothelial cell proliferation. Briefly, human umbilical vein endothelial cells (HUVEC) were seeded in 6-well plates at a density of 2500/cm². At mid-log phase the

cells were treated with a test compound or vehicle control. Forty-eight (48) hours later the cells were detached from the plate and counted using a coulter counter. Viability tests were conducted using trypan blue. The data is expressed as percent inhibition based on the control number of endothelial cells counted. The results are illustrated in Table 1 below:

5

TABLE 1

Concentration [μ M]	% Inhibition of Endothelial Cell Proliferation					
	Compound A	Compound B	Compound E	Vitamin E	Naproxen	Compound G
1.0	6.7	5.0	25	0	0	4.3
5.0	25.5	13.9	48	0	1.9	8.0
10	43.4	47.7	88	1	1.0	35.1
25	55.2	60.5	91	--	--	65.5

The data of Table 2 demonstrates the endothelial cell anti-proliferative efficacy of representative compounds of the present invention, as compared to naproxen and vitamin E.

10

Example 10

Representative compounds of the present invention were assayed for their efficacy in inhibiting ^3H -thymidine uptake in DNA as a measure of DNA synthesis (R.I. Freshney, Culture of Animal Cells, 3rd Edition, John Wiley and Sons, N.Y., N.Y., pages 277-278 (1994)). Briefly, human lung microvascular endothelial cells in mid-log phase were exposed to either a representative compound of the present invention or the vehicle (1.0% DMSO) for 18 hours. Cells were then incubated with ^3H -thymidine for another 6 hours. DNA synthesis was stopped by the addition of cold 5% TCA solution and the relative synthesis assessed by measuring ^3H -thymidine incorporated into the acid-insoluble product. The data is expressed as percent inhibition of uptake based on tritium counts in the vehicle control reactions. The results are presented in Table 2 below:

20

25

TABLE 2

Concentration [μ M]	% Inhibition of 3 H-thymidine Uptake	
	Compound A	Compound B
5.0	16.3	36.9
10	25.7	63.1
15	57.4	---
20	82.9	---
25	96.5	97.9

- 5 The data of Table 2 demonstrates the efficacy of representative compounds of the present invention in inhibiting endothelial cell proliferation based on the inhibition of DNA synthesis.

Example 11

- 10 Representative compounds of the present invention were assayed for their efficacy in inhibiting angiogenesis in a chorioallantoic membrane (CAM) model (See, McNatt, et al., *Angiostatic Activity and Metabolism of Cortisol in The Chorioallantoic Membrane (CAM) of the Chick Embryo*, Journal of Steroid Biochemistry and Molecular Biology, volume 42, No. 7, pages 687-693 (1992)). Briefly, 10 μ g of the test compound or reference compound
- 15 (tetrahydrocortisol) were suspended in a liposome/agarose bead and placed on the CAM of a 5-6 day chicken embryo. Following 2 days of incubation, the CAMs were scored for relative angiostatic activity by comparing percent responding embryos per nanomole test compound to percent responding embryos for the reference compound. The results are illustrated in Table 3 below:

TABLE 3

Compound	RAF *
Tetrahydrocortisol	1.00 (reference)
Compound A	0.10
Compound B	1.06
Compound E	1.78
Compound G	1.21

* Relative Angiostatic Factor

- 5 As Table 3 demonstrates, representative compounds of the present invention show angiostatic efficacy in the CAM model.

Example 12

Representative compounds of the present invention were assayed for their efficacy in
10 inhibiting angiogenesis *in vivo*, in a rabbit model of lipopolysaccharide (LPS) induced corneal neovascularization. Briefly, the test compound and LPS (a stimulus for initiating neovascularization) are incorporated into separate Elvax-40 pellets as described in D. BenEzra, *The Rabbit Cornea. A Model for the Study of Angiogenic Factors*, in "Ocular Circulation and Neovascularization, Documenta Ophthalmologia, Proceedings Series 50,
15 pages 335-340 (1987) and D. BenEzra, *Thrombospondin and In Vivo Angiogenesis Induced by Basic Fibroblast Growth Factor or Lipopolysaccharide*, Investigative Ophthalmology and Visual Sciences, volume 34, No. 13, pages 3601-3608 (1993), which are surgically implanted into rabbit cornea. The area covered by new vessel formation in response to LPS is measured and suppression of neovascularization by test compounds is estimated at the
20 end of the test period. The data is expressed as a relative area units in relation to the Elvax control (100). The results are illustrated in Table 4 below:

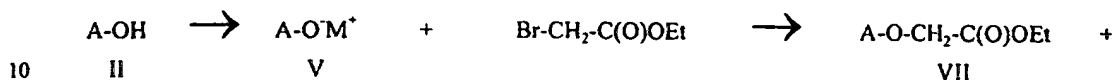
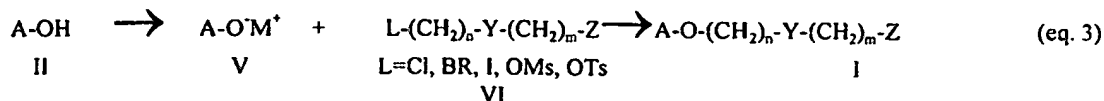
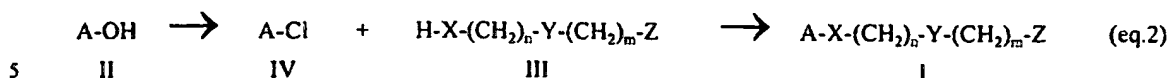
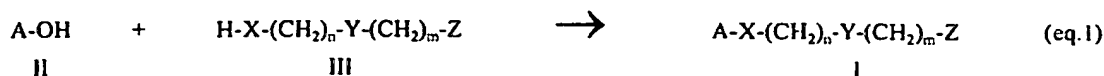
TABLE 4

Days	Relative Area of Neovascularization						
	Elvax control	Naproxen	Compound E	Compound A	Compound C	Hydrocortisone hemisuccinate	Compound F
4	100	88	99	66	102	0	92
9	100	93	76	54	57	1.5	85
15	100	91	88	48	41	0.6	30
22	100	80	115	103	60	4.9	39

The data of Table 4 demonstrate the efficacy of representative compounds of the present invention in in vivo inhibition of neovascularization.

Some of the compounds of the present invention may contain a nonsteroidal anti-inflammatory agent (NSAIA) component, and others may contain a calcium channel blocker (flunarizine) component. These individual moieties may add additional pharmaceutical benefit to the angiostatic efficacy of the compounds of the present invention.

The compounds of the present invention are synthesized by known methods in the art. Compounds containing a non-steroidal anti-inflammatory agent (flurbiprofen or naproxen) can be made by methods illustrated in Scheme 1 and 2, and Examples 13-16. Compounds containing a flunarizine moiety may be made by methods disclosed in commonly assigned PCT Patent Publication No. WO/9515958, the entire contents of which are hereby incorporated by reference. Other compounds of the present invention are commercially available from: Sigma Chemical Co. (St. Louis, Missouri) and Aldrich Chemical Co. (Milwaukee, Wisconsin).

Scheme 1

The conversion of the carboxylic acid containing nonsteroidal anti-inflammatory agents (II) to esters or amides (I) may be carried out by the following methods:

(i) As illustrated in equation 1 above, carboxylic acids (II) may be reacted with the appropriate amine or alcohol derivative (III) in the presence of a coupling reagent, such as dicyclohexylcarbodiimide or 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide HCl, and 4-dimethylamine pyridine or 1-hydroxybenzotriazole, in an inert organic solvent, such as acetonitrile or tetrahydrofuran, and at a temperature from 0°C to 50°C.

(ii) As illustrated in equation 2 above, carboxylic acids (II) may be converted to acid chlorides (IV) by reacting them with a reagent such as thionyl chloride or oxalyl chloride, in the presence of an inert solid or neat, at a temperature from 0°C to 80°C. The resulting acid chloride (IV) may be reacted with the desired amine or alcohol (III) in an inert solvent such as tetrahydrofuran, in the presence of pyridine or a tertiary amine, such as triethylamine.

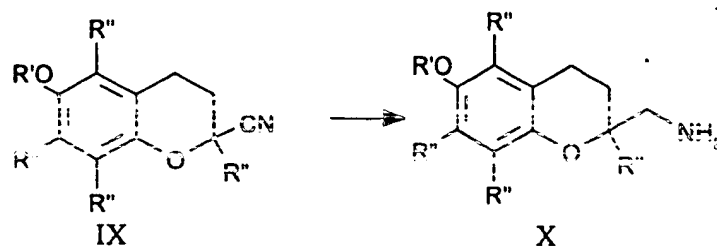
(iii) As illustrated in equation 3 above, esters (I) may be formed by reacting carboxylate anions (V), formed by reacting the carboxylic acid (II) with a base such as sodium hydride, with a halide (iodide, bromide, chloride) or sulfonate (mesylate, tosylate) (VI), in a solvent such as acetonitrile or dimethylformamide, at a temperature from 0°C to 100°C.

(iv) As illustrated in equation 4 above, amides (I) may be prepared by reacting carboxylate anions (V), formed by reacting carboxylic acid (II) with a base such as sodium hydride, with ethyl bromoacetate. The resulting ester (VII) is reacted with the desired amine (VIII), neat or in an inert solvent, such as acetonitrile or dimethylformamide, at a temperature from 0°C to 100°C.

The intermediate compounds (X) of Scheme 2 below, which can be used as compounds (III) and (VIII), were prepared using the general methods described in Journal of Organic Chemistry, volume 54, pages 3282-3292, (1989). The nitrile (IX) can be reduced using a reagent such as lithium aluminum hydride to afford the amine (X), which may be isolated as the hydrochloride salt.

The use of certain protecting groups and deprotection steps may be necessary, as will be appreciated by those skilled in the art.

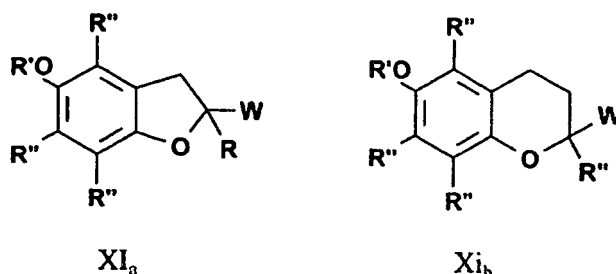
Scheme 2



Compounds of formula (I) may exist as mixtures of stereoisomers. The preparation of the individual stereoisomers may be effected by preparing and resolving the acids (II), by known methods, and then using a single stereoisomer as starting material. Compounds

(III), (VI) and (VIII) may be prepared as single stereoisomers from compounds of formula (XI_{a-b}), shown in Table 5 below, using known methods:

Table 5



wherein:

W is $(\text{CH}_2)_p\text{-Q}$;

p is 0-1;

Q is CH_2OH or CO_2H ;

R' is H, $\text{C}(\text{O})\text{R}$, $\text{C}(\text{O})\text{NR}_2$, PO_3^- , or SO_3^- ; and

R'' is H or $\text{C}_1\text{-C}_6$ alkyl.

The alcohols (XI_{a-b}) may be resolved by forming esters with optically active carboxylic acids, separating the diastereomers, and then hydrolyzing the resolved diastereomers. The corresponding carboxylic acids (XI_{a-b}) may be resolved by forming an ester with an optically active alcohol, separating the diastereomers, and then hydrolyzing the resolved diastereomers. Or, the carboxylic acids (XI_{a-b}) may be resolved by forming an amine salt with an optically active amine. Separation by recrystallization and neutralization of the resolved carboxylic acid salt may be utilized to provide the resolved carboxylic acid. Resolution of the esters and amides (I) may also be effected using chromatographic techniques known to those skilled in the art.

The amines of formula (I), where Y is NR, may be converted to amine salts by reacting the amine with acids of sufficient strength to produce an organic or inorganic salt.

The pharmaceutically acceptable anions include: acetate, bromide, chloride, citrate, maleate, fumarate, mesylate, phosphate, sulfate and tartrate.

Methods of synthesizing the compounds formula (I) are further illustrated by the following examples:

5

Example 13

Synthesis of N-[(6-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-1-benzo[1,2-b]pyran-2-yl)methyl] 2-(6-methoxy-2-naphthyl)propionamide

The intermediate, (6-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-1-benzo[1,2-b]pyran-2-yl)methylamine, was first synthesized:

A 1 molar (M) ethereal solution of lithium aluminum hydride (Aldrich, 32.4 mL, 32.43 mmol) was added slowly over a 5 minute period to a chilled, (4-6°C) stirring solution of (2-cyano-6-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-1-benzo[1,2-b]pyran in tetrahydrofuran (50 mL). After 2 hours, the reaction mixture was quenched by the slow sequential addition of 10% aqueous tetrahydrofuran (30 mL), 15% sodium hydroxide (10 mL) and then water (20 mL), while stirring. The resulting suspension was filtered through celite, and the celite pad was washed with ethyl ether (400 mL). The organic layer was separated, dried (Na₂SO₄), and concentrated in vacuo, resulting in a residue. A 1 M ethereal solution of hydrochloride was then added to a solution of the residue in ethyl ether (100 mL), a solid formed, and the solid was then collected by filtration and washed with ethyl ether to give 2.31 g (65.4% yield) of a white solid. The product was used crude in the next reaction.

¹H-NMR (DMSO-d₆/TMS): 1.15 (s, 3H), 1.75 (t, 2H), 1.99 (s, 6H), 2.01 (s, 3H), 2.54 (t, 2H), 2.98 (s, 2H).

MS (CI): 236 (m+1).

The hydrochloride salt of (6-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-1-benzo[1,2-b]pyran-2-yl)methylamine (0.30 g, 1.10 mmole) and 6-methoxy- α -methyl naphthaleneacetic acid (Aldrich, 0.28 g, 1.21 mmole) were stirred in the presence of dimethylaminopyridine (Aldrich, 0.26 g, 2.20 mmole) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (Janssen Chimica-Spectrum, 0.21 g, 1.10 mmole), in tetrahydrofuran (4.0 mL) under an atmosphere of nitrogen. After stirring 17 hours at ambient temperature, the reaction mixture was diluted with ethyl acetate (70 mL), washed with water (2x 15 mL), followed by brine (15 mL) and then dried (sodium sulfate). The mixture was concentrated in vacuo and the residue subjected to flash chromatography (silica gel, 100-50:0-50, v:v, hexanes:ethyl acetate). The appropriate fractions were concentrated in vacuo, and the resulting crystalline foam suspension was then washed in hexanes to give 0.28 g (58.3% yield) of N-[(5-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-1-benzopyran-2-yl)methyl]-2-(6-methoxy-2-naphthyl)propionamide as a white amorphous solid.

¹H-NMR (CDCl₃) δ 1.03-1.08 (d, 3H), 1.57-1.64 (m, 6H), 1.70 (t, 2H), 2.04-2.05 (m, 6H), 2.48-2.51 (m, 2H), 3.16-3.58 (m, 2H), 3.74 (q, 1H), 3.91 (s, 3H), 4.91 (br s, 1H), 5.751 (t, 1H), 7.01-7.19 (m, 2H), 7.29-7.40 (t, 1H), 7.52-7.81 (m, 3H).

Elemental Analysis: Calculated for C₂₈H₃₃NO₄

Calculated: C, 75.14; H, 7.43; N, 3.13.

Found: C, 75.04; H, 7.50; N, 2.97.

Melting point: 67-70°C.

Example 14

Synthesis of 2-(6-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-benzo[1,2-b]pyran-2-yl)ethyl 2-(6-methoxy-2-naphthyl)propionate

A solution of 1,3-dicyclohexylcarbodiimide (Aldrich, 0.89 g, 4.31 mmol) in acetonitrile (25 mL), was added dropwise to a stirring slurry of (+)-6-methoxy- α -methyl-2-naphthaleneacetic acid (Aldrich, 0.90 g, 3.91 mmol), 2-hydroxy-2,5,7,8-tetramethyl-3,4-

dihydro-2H-benzo[1,2-b]pyran-2yl)ethanol (0.98 g, 3.91 mmol, USP 5,266,709 column 45) and 1-hydroxybenzotriazole hydrate (Aldrich, 0.59 g, 4.31 mmol), in acetonitrile (50 mL). After stirring for 18 hours, the reaction mixture was concentrated in vacuo. The residue was partitioned between water (30 mL) and methylene chloride (30 mL). The layers were separated, and the aqueous layer was extracted with methylene chloride (2 x 20 mL). The combined organic extracts were washed with water (20 mL), then dried (magnesium sulfate) and concentrated in vacuo. Flash chromatography (silica gel, 2:8, v:v, ethyl acetate:hexanes) of the residue afforded a white solid upon the concentration of the appropriate fractions. The white solid was recrystallized from an ethyl acetate-hexanes mixture to give 0.60 g (33.1% yield) of 2-(6-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-benzo[1,2-b]pyran-2yl)ethyl 2-(6-methoxy-2-naphthyl)propionate, a mixture of diastereomers, as a white solid.

¹H NMR (CDCl₃) δ 1.1 (d, 3H), 1.6-1.5 (m, 3H), 1.6 (m, 2H), 1.9 (m, 2H), 2.0 (s, 6H), 2.1 (s, 3H), 2.4 (t, 2H), 3.8 (q, 2H), 3.9 (s, 3H), 4.2 (s, 1H), 4.1-4.4 (m, 2H), 7.1-7.7 (m, 6H).

Elemental Analysis: Calculated for C₂₉H₃₄O₅

Calculated: C, 75.30; H, 7.41.

Found: C, 75.24; H, 7.46.

Melting Point: 99.5-101.5°C.

20

Example 15

Synthesis of 2-(5-hydroxy-2,4,6,7-tetramethyl-3,4-dihydro-benzo[1,2-b]furan-2-yl)ethyl 2-(6-methoxy-2-naphthyl)propionate

A solution of 2-(5-hydroxy-2,4,6,7-tetramethyl-2,3-dihydrobenzo[1,2-b]furan-2-yl)ethanol (1.30 g, 5.51 mmol) and 6-methoxy- α -methyl naphthaleneacetic acid (Aldrich, 1.39 g, 6.06 mmol) was stirred in the presence of dimethylaminopyridine (0.67 g, 5.51 mmol) and 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (1.06 g, 5.51 mmol), in tetrahydrofuran (25 mL). The reaction mixture was stirred at ambient temperature under nitrogen for 24 hours, diluted with ethyl acetate (150 mL), washed with water (2x 40 mL)

and then brine (30 mL). The organic extract was dried (sodium sulfate) and concentrated in vacuo. The residue was subjected to flash chromatography (silica gel, 100-50:0-50, v:v, hexanes:ethyl acetate), and the appropriate fractions were combined to give 1.84 g (74.5% yield) of a foam residue. Fractional crystallization and recrystallization from methylene chloride-hexanes gave 0.40 g (13.0% yield) of white solid.

¹H-NMR (CDCl₃): 1.34 (s, 3H), 1.54-1.57 (d, 3), 1.99 (t, 2H), 2.01 (s, 3H), 2.05 (s, 3H), 2.10 (s, 3), 2.73-2.81 (d, 1), 2.90-2.97 (d, 1), 3.77-3.89 (q, 1H), 3.91 (s, 3H), 4.102 (s, 1H, 4.165-4.29 (m, 2H), 7.10-7.16 (m, 2H), 7.35-7.40 (m, 1H), 7.64-7.70 (m, 2H).

Elemental Analysis: Calculated for C₂₈H₃₂O₅ · 0.1 mole CH₂Cl₂.

10 Calculated: C, 73.84; H, 7.10.

Found: C, 73.85, 73.83; H, 7.12.

Melting point: 129.5-131°C.

Example 16

15 Synthesis of 2-(6-hydroxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-benzo [1,2-b]pyran-2yl)ethyl 2-(3-fluoro-4-phenyl-phenyl)propionate

The intermediate, 2-(6-benzyloxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-benzo[1,2-b]pyran-2yl)ethyl 2-(3-fluoro-4-phenyl-phenyl)propionate, was first synthesized:

A solution of flubiprofen (Sigma, 2.0 g, 8.2 mmol), 2-(6-benzyloxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-benzo[1,2-b]pyran-2-yl)ethanol (2.4 g, 8.2 mmol) 1-hydroxybenzotriazole hydrate (Aldrich, 2.4 g, 13.9 mmol) and 1-(3 dimethylaminopropyl) 3 ethyl-carbodiimide hydrochloride (Aldrich, 2.8 g, 12.3 mmol), in acetonitrile (40 ml), was stirred at ambient temperature. After 72 hours, the reaction mixture was concentrated in vacuo and the residue partitioned between water and methylene chloride. A solid formed which was removed by filtration and discarded. The layers were separated and the aqueous layer was extracted with methylene chloride (2 x 25 ml). The combined organic extracts were then dried (magnesium sulfate) and concentrated in vacuo. The residue was chromatographed

(silica gel, 2:8, v:v, ethyl acetate:hexane). Concentration of the appropriate fractions afforded 3.0 g (64% yield, mixture of stereoisomers) of the product as a clear oil.

¹H NMR (CDCl₃) d: 1.23-1.27 (m, 3H), 1.53-1.57 (m, 3H), 1.75 (m, 2H), 1.95 (m, 2H),
5 2.08 (s, 3H), 2.14 (s, 3H), 2.21 (s, 3H), 2.55 (t, 3H), 3.75 (m, 2H), 4.3 (m, 1H), 4.65 (s,
2H), 7.1-7.7 (m, 13H).

A solution of 2-(6-benzyloxy-2,5,7,8-tetramethyl-3,4-dihydro-2H-benzo
[1,2-b]pyran-2-yl)ethyl 2-(3-fluoro-4-phenyl-phenyl)propionate in ethyl acetate was treated
with 10% palladium on charcoal (Aldrich, 0.5 g). The resulting mixture was hydrogenated
10 on a Parr Apparatus [initial pressure 60 pounds/inch² (psi)]. After 18 hours, the reaction
mixture was filtered, and the resulting solution concentrated in vacuo. The residue was
subjected to flash chromatography (silica gel, 2:8, v:v, ethyl acetate:hexane). Concentration
of the appropriate fractions afforded a clear oil. Hexane was added to the oil and a white
solid formed upon standing. The white solid was collected by filtration to afford 0.91 g
15 (36% yield) of 2-6-hydroxy-2,5,7,8-tetra methyl-,4-dihydro-H-benzo[1,2-b]pyran-yl)ethyl
2-(3-fluoro-4-phenyl-phenyl) propionate as a mixture of stereoisomers.

¹H NMR (CDCl₃) d: 1.22-1.23 (m, 3H), 1.51-1.55 (m, 3H), 1.65-1.8 (m, 2H), 1.85-2.00 (m,
2H), 2.08 (s, 6H), 2.14 (s, 3H), 2.57 (t, 2H), 3.75 (q, 1H), 4.1-4.5 (m, 2H), 7.10-7.65 (m,
8H).

20 Elemental Analysis: Calculated for C₃₀H₃₃FO₄.

Calculated: C, 75.60; H, 6.98.

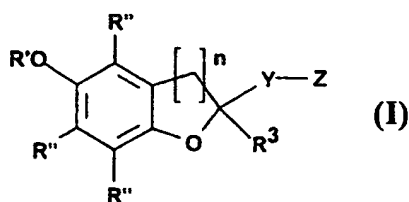
Found: C, 75.69; H, 7.01.

Melting point: 85-87°C.

The invention in its broader aspects is not limited to the specific details shown and described above. Departures may be made from such details within the scope of the accompanying claims without departing from the principles of the invention and without sacrificing its advantages.

What is claimed is:

1. A composition for the treatment of pathological neovascularization comprising an effective amount of a compound according to formula (I):



wherein:

n is 1 or 2;

R is H, C₁-C₆ alkyl or C₃-C₆ cycloalkyl;

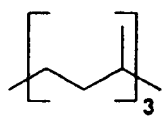
Y is H, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, O, NR, C(R)₂, CH(OH) or S(O)_n;

n' is 0 to 2;

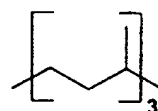
R' is H, C(O)R, C(O)N(R)₂, PO₃⁻, SO₃⁻ or HO₂C(CH₂)₂(C=O)---;

R'' is H or C₁-C₆ alkyl;

R³ is H, C₁-C₆ alkyl, (CH₂)_q(OH), ---C(=O)O(CH₂)_qCH₃ or

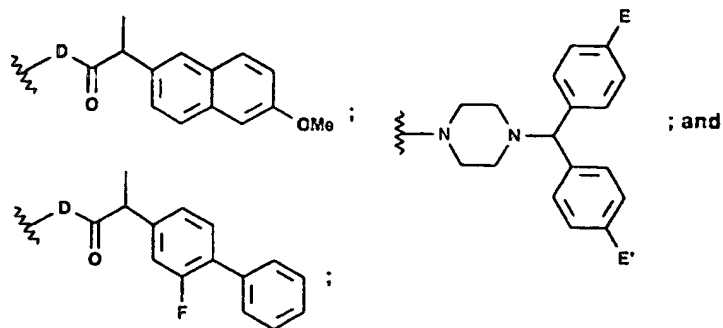


; provided that R' can not be H, when R³ is



q is 1 to 10; and

Z, if present, is H, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, or selected from the group consisting of:



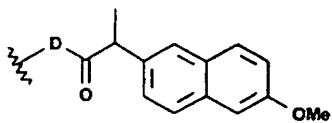
wherein:

D is O or NR; and

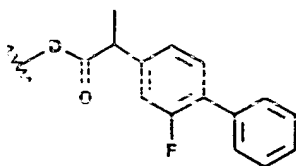
E and E' are independently H, F or Cl; and pharmaceutically acceptable salts thereof.

2. The composition according to Claim 1, wherein: R is H, R' is H; R'' is CH₃; R³ is CH₃; and Y is C₁-C₂ alkyl.

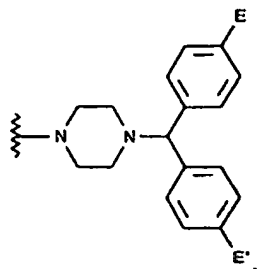
3. The composition according to Claim 1, wherein Z is:



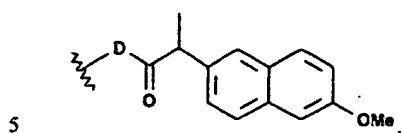
4. The composition according to Claim 1, wherein Z is:



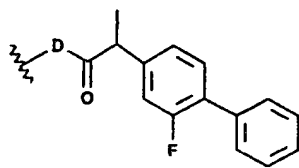
5. The composition according to Claim 1, wherein Z is:



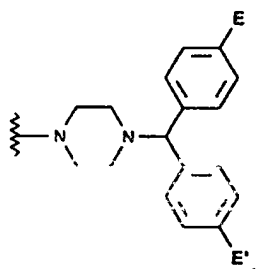
6. The composition according to Claim 2, wherein Z is:



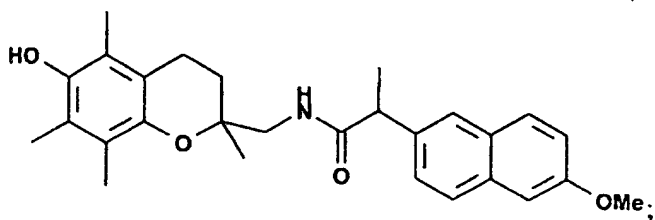
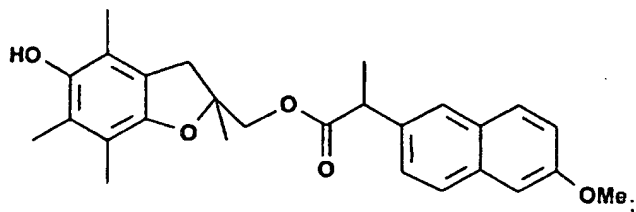
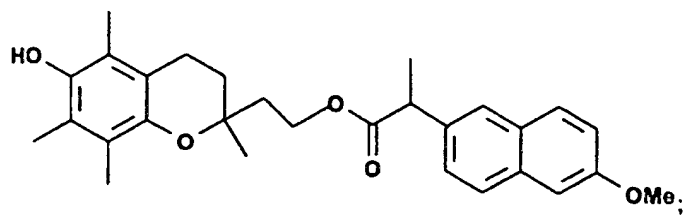
7. The composition according to Claim 2, wherein Z is:



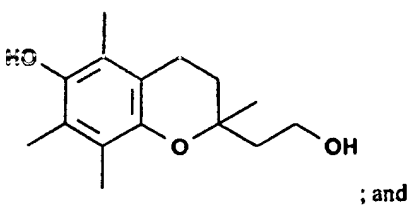
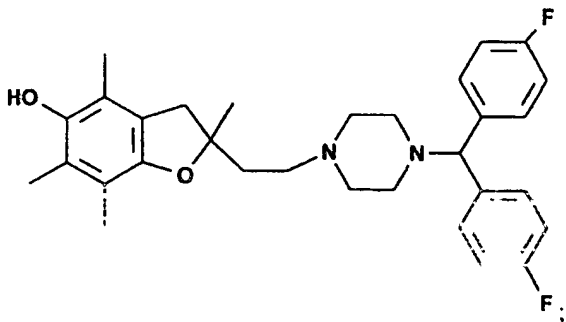
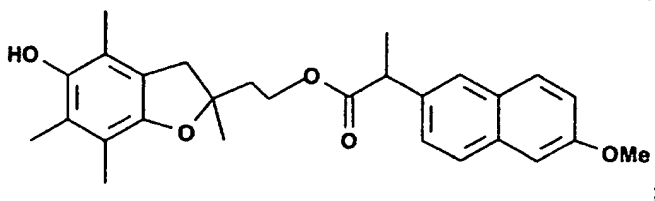
- 10 8. The composition according to Claim 2, wherein Z is:



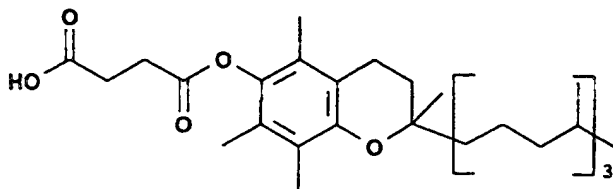
9. The composition according to Claim 1, wherein the compound is selected from the group consisting of:



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; and

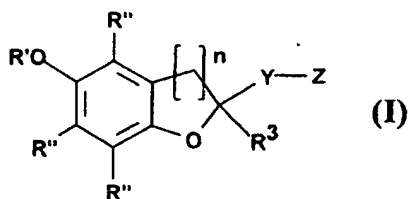


10. The composition according to Claim 1, wherein the composition comprises a physiologically balanced irrigating solution.

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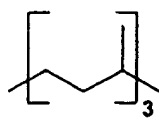
11. The composition according to Claim 1, wherein the composition is used to treat glaucoma filtration surgery bleb failure, pterygium, hyperkeratosis, cheloid formation and polyp formation.

10 12. A method for treating pathological neovascularization which comprises administering to a human patient an effective amount of a pharmaceutical composition comprising a compound according to formula (I):

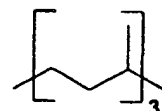


wherein:

- 15 n is 1 or 2;
 R is H, C₁-C₆ alkyl or C₃-C₆ cycloalkyl;
 Y is H, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, O, NR, C(R)₂, CH(OH) or S(O)_n;
 n' is 0 to 2;
 R' is H, C(O)R, C(O)N(R)₂, PO₃⁻, SO₃⁻ or HO₂C(CH₂)₂(C=O)---;
 20 R'' is H or C₁-C₆ alkyl;
 R³ is H, C₁-C₆ alkyl, (CH₂)_q(OH), ---C(=O)O(CH₂)_qCH₃ or



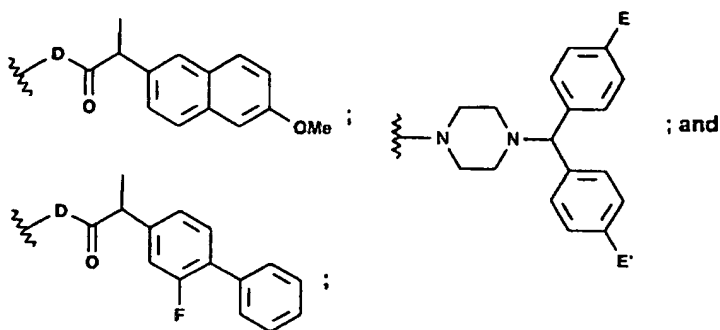
; provided that R' can not be H, when R³ is



;

q is 1 to 10; and

Z, if present, is H, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, or selected from the group consisting of:



5

wherein:

D is O or NR; and

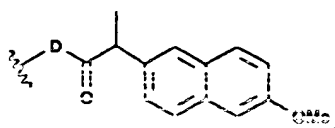
E and E' are independently H, F or Cl; and pharmaceutically acceptable salts thereof.

10

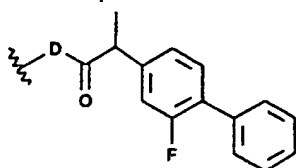
13. The method according to Claim 12, wherein: R is H, R' is H; R'' is CH₃; R³ is CH₃; and Y is C₁-C₂ alkyl.

15

14. The method according to Claim 12, wherein Z is:

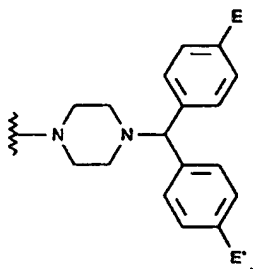


15. The method according to Claim 12, wherein Z is:

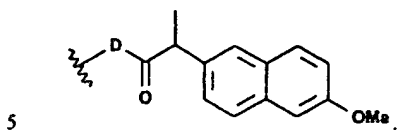


20

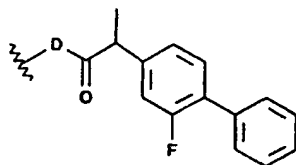
16. The method according to Claim 12, wherein Z is:



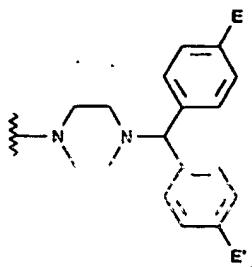
17. The method according to Claim 13, wherein Z is:



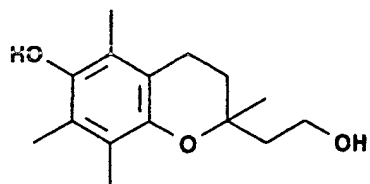
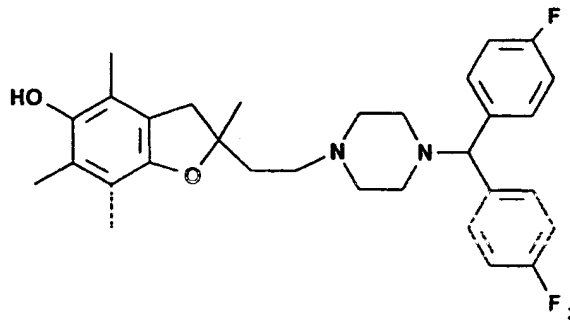
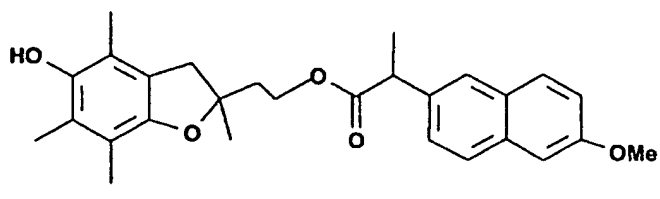
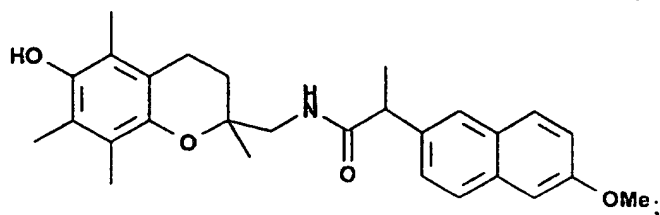
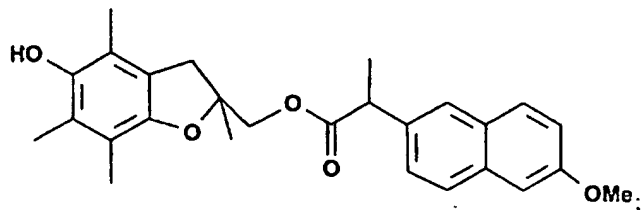
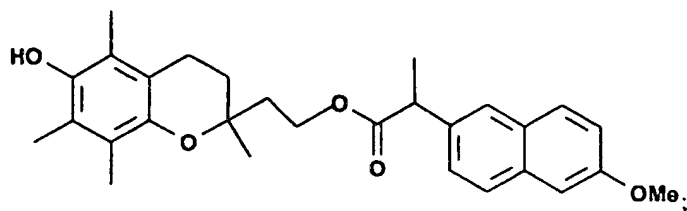
18. The method according to Claim 13, wherein Z is:



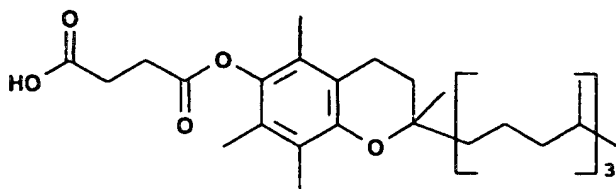
10 19. The method according to Claim 13, wherein Z is:



20. The method according to Claim 12, wherein the compound is selected from the group consisting of:



; and



21. The method according to Claim 12, wherein the composition comprises a physiologically balanced irrigating solution.

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22. The method according to Claim 12, which comprises administering the composition to a human patient to treat glaucoma filtration surgery bleb failure, pterygium, hyperkeratosis, cheloid formation and polyp formation.

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/US 97/08066

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/35 A61K31/355 A61K31/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 15958 A (ALCON LABORATORIES, INC.) 15 June 1995 cited in the application see page 6, line 18 - page 7, line 14 see claims 17-27,33,50-53 ---	1,2,5, 8-11
X	EP 0 572 190 A (SANTEN PHARMACEUTICAL CO., LTD.) 1 December 1993 see abstract see page 3, line 11 - line 12 ---	1,2,9,11
X,P	EP 0 732 329 A (SHUDO, KOICHI) 18 September 1996 see abstract see page 14 - page 15 see claims 3-7; examples 1,2 --- -/--	1,2

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

17 September 1997

Date of mailing of the international search report

3 0. 09. 97

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Alvarez Alvarez, C

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 97/08066

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 413 668 A (BIOMEDICA FOSCAMA INDUSTRIA CHIMICO-FARMACEUTICA S.P.A.) 20 February 1991 see claims 1,19 ---	1,9
X	US 5 114 957 A (SHELDON S. HENDLER ET AL.) 19 May 1992 see column 2, line 22 - line 27 see column 2, line 62 ---	1,9
A	US 5 424 321 A (MARK R. HELLBERG ET AL.) 13 June 1995 see column 4 - column 5 see column 15, line 52 - line 57 see column 16, line 58 - line 62 see column 17, line 8 - line 24 see example 1 -----	1,10,11

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 97/08066

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 12-22 is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.

PCT/US 97/08066

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9515958 A	15-06-95	AU 1336895 A BR 9406080 A CA 2153979 A CN 1117292 A EP 0682664 A FI 953748 A JP 8507546 T NO 953093 A US 5646149 A	27-06-95 06-02-96 15-06-95 21-02-96 22-11-95 07-08-95 13-08-96 09-10-95 08-07-97
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EP 413668 A	20-02-91	AT 131164 T AU 634570 B AU 6128090 A CA 2023522 A CN 1049499 A,B CS 9004023 A DE 69023980 D DE 69023980 T ES 2080821 T FI 92198 B JP 3236383 A NO 175819 B RU 2068845 C US 5114966 A	15-12-95 25-02-93 21-02-91 19-02-91 27-02-91 15-01-92 18-01-96 01-08-96 16-02-96 30-06-94 22-10-91 05-09-94 10-11-96 19-05-92
US 5114957 A	19-05-92	NONE	
US 5424321 A	13-06-95	WO 9641805 A AU 2827495 A	27-12-96 09-01-97